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Lipid metabolism during infection and endotoxemia

ROBERT W. WANNEMACHER, Jr, JUDITH G. PACE and HAROLD A. NEUFELD

U. S. Army Medical Research Institute of Infectious Diseases, Fort Detrick, Frederick, MD 21701, U.S.A.

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I. INTRODUCTION

Of three major nutrients, only lipid can be stored in large quantities in most vertebrates. This is due in part to the fact that the body contains specialized mesenchymal cells, 'adipocytes,' that are devoted solely to the function of storing fat. Therefore, lipid in the form of triglyceride is the major storage form of energy in the human body. In addition to being the major storage form of energy and metabolic fuel, lipids function as structural components of cell membranes, emulsifying agents, and precursors for the synthesis of sterols, four vitamins and prostaglandins. Since lipids are organic compounds that are poorly soluble in water, a complex system has been developed for the absorption and transport of lipids throughout the body. A number of excellent reviews (Schumaker and Adams, 1969; Wakil, 1970; Gurr and James, 1971; Masoro, 1977) have been written on various aspects of lipid metabolism; therefore, only a brief description of the subject will be covered in this chapter.

Ordinary dietary fats are emulsified by the bile secretions (conjugated bile acids, phosphatidylcholine and cholesterol) into mixed micelles in the duodenum of the small intestine. In the micellar form the lipids can be hydrolyzed by enzymes secreted from the exocrine pancreas to 2-monoglycerides, fatty acids and cholesterol. These hydrolyzed products are absorbed by passive diffusion into the mucosal cells of the intestine. Within these cells the absorbed fatty acids and 2-monoglycerides are resynthesized into triglycerides. These triglycerides are utilized to form two micellar lipoproteins, 'chylomicrons' and 'very low-density lipoproteins' (VLDL), which are secreted into the lymph and pass from it into venous blood. The triglyceride content of these lipoproteins is removed by the action of a hydrolytic enzyme, lipoprotein lipase (EC 3.1.1.34), and the released fatty acids are taken up by various tissues of the body. This enzyme is present in capillary walls and in such tissues as adipose tissue, mammary gland and heart. However, the majority of the absorbed dietary triglycerides are deposited in liver and adipose tissue.

Long-chain triglycerides are a major lipid component of most of the food consumed by humans. Recently, medium-chain triglycerides (containing 8- and 10-carbon fatty acids almost exclusively) have been used in certain therapeutic diets. In contrast to the long-chain triglycerides, medium-chain triglycerides are absorbed intact either onto the mucosal cell villi or directly into the cells, where they are hydrolyzed completely to fatty acids and glycerol by intestinal cell microsomal lipase. The medium-chain fatty acids pass directly into the portal vein, where they bind physically to plasma albumin and are delivered directly to the liver as fatty acids by the portal circulation.

Fat is stored mainly in the adipocytes in the form of triglyceride. Within these cells, the glycerol moiety is derived from glucose. While adipocytes can synthesize some fatty acids from glucose, the majority of fatty acids are derived

from circulating blood triglycerides contained in either chylomicrons or VLDL. These lipoprotein triglycerides must be hydrolyzed by lipoprotein lipase so that their fatty acid content can enter into the adipose cell for the resynthesis of triglycerides. When calories are adequate or in excess and the individual is resting, fat accumulates in adipose tissue. Conversely, free fatty acids (FFA) are mobilized in large amounts from adipose tissue during periods of fasting, anxiety, or physical exertion. Fatty acid mobilization in the adipocyte involves hydrolysis of triglyceride by activated triglyceride and monoglyceride lipase. The resulting FFA are released from adipose tissue and bind physically to plasma albumin, by which they are transported to heart, skeletal muscle, liver and other tissues. In all organs but the brain, the FFA are either oxidized as a source of energy or incorporated into esterified lipids of the tissues.

With the exception of chylomicrons, the hepatocyte is the major source of lipoproteins, the major lipid transport macromolecules. Once FFA enter the liver cell, they are activated by formation of the acyl-CoA thioester. Long-chain acyl-CoA can either (1) enter synthetic pathways for the formation of triglycerides and subsequently lipoproteins, phospholipids (phosphoglycerides and sphingolipids) and/or glycolipids or (2) be transported into mitochondria and peroxisomes to undergo β-oxidation with the resulting formation of acetyl-CoA and generation of ATP. The resulting acetyl-CoA can enter the Krebs cycle or be utilized for synthesis of ketone bodies (acetoacetate and β-hydroxybutyrate), fatty acids and/or cholesterol. Therefore, the liver plays a key role in the clearance and metabolism of both dietary and endogenous lipids. Thus, the adipose tissue, intestine and liver, are the keystones of storage, mobilization and metabolism of lipids.

From this brief description it is obvious that lipid metabolism is complex and plays a key role in maintaining homeostatis of the host. Since infectious disease stimulates a severe catabolic response and elevation in body temperature (Wannemacher and Beisel, 1977), it is not surprising to anticipate that it will also cause some marked alterations in lipid metabolism of the host.

II. SERUM LIPID CONCENTRATION DURING INFECTIOUS DISEASE

Infection-related changes in serum lipid profiles are quite variable and appear to be dependent upon an algebraic summation of multiple factors including severity of illness, nutrient-hormonal effects, target organs for a specific microorganism, effects on intestinal absorption and the lipid precursors needed for replication of the invading microorganism (Gallin et al., 1969; Beisel and Fiser, 1970; Blackburn, 1977). Further, from several sequential studies (Fiser et al., 1972a; Lees et al., 1972; Saudek, 1977), it is apparent that the changes in the serum lipid profiles could be quite different depending on whether the measurements are made during the incubation, illness, or recovery phase of the

infection. Despite these complications, a definite pattern of change in serum lipid profiles has been observed which are characteristic for individual infectious diseases.

A. *Serum free fatty acids*

While serum FFA have been observed to increase during some gram-negative infections in man (Gallin et al., 1969; Beisel and Fiser, 1972a), this lipid component is usually unaltered or decreased during severe sepsis in other bacterial and viral infections as well as in endotoxemia in man and experimental animals (Fiser et al., 1972a, 1974; Lees et al., 1972; Neufeld et al., 1976). Alterations in serum FFA concentrations could represent changes in the rate of lipolysis and release from adipocytes and/or utilization by tissues, such as skeletal muscle, heart and liver. Rates of lipolysis, FFA release, or reesterification in epididymal fat pads in rats were not altered during gram-positive, *Streptococcus pneumoniae* infection compared to fasted controls (Wannemacher et al., 1979c). In contrast, Ryan et al. (1974) did observe a possible decrease in the rate of lipolysis of epididymal fat pads during experimental peritonitis in rats. While serum FFA were reduced in both experimentally induced infections, the mechanisms that brought about this change were apparently different for the two. Despite a 48% decrease in serum FFA, Carpentier et al. (1979) found a 2—3-fold increase in glycerol turnover in infected patients. Thus, serum FFA concentrations do not appear to be a good indicator of rates of lipolysis or tissue utilization of these metabolites. Infection-related alterations in lipolysis and tissue utilization of FFA seem to be variable and are affected by the severity and stage of illness.

Serum FFA content can also be influenced by the concentration of circulating albumin. Since long-chain fatty acids are highly insoluble in physiological fluids, they must form fatty acid-albumin complexes for transport in the circulatory system. This interaction takes place via electrostatic and hydrophobic forces, with the latter being the main contributor to the binding energy (Spector, 1975). Studies on the interaction of albumin with fatty acids and ionic detergents have revealed about 10 binding sites of relatively high affinity for these ligands (Steinhardt and Reynolds, 1969). In the classic work of Goodman (1958), the binding isotherms for palmitate to human serum albumin indicated the presence of two strong binding sites, five moderately strong ones and a number of low-affinity sites. More recently, it has been shown (Spector, 1975) that the equilibrium constant for the first binding site is 10-times that of the second one and that the next binding sites have another 10-fold decrease in equilibrium constant. In the human and most experimental animals, the FFA/albumin molar ratio rarely exceeds 4 and for the most part is between 0.5 and 2 (Frederickson and Gordon, 1958; Havel et al., 1967). Therefore, the first four highest affinity FFA-albumin binding sites are the only ones that have physiological significance in the regulation of lipid metabolism. On the basis of these

results, one can calculate that if one equivalent of palmitic acid is added to a solution of albumin, about 75% will become bound to the strongest binding site. The remaining 25% will be distributed among the other binding sites, mostly to the second one. As the FFA concentration presented to albumin is increased, binding sites of lower affinity become saturated with this FFA. It has been demonstrated that the FFA on the low-affinity binding sites of albumin exchange more readily with the hepatic cytoplasmic-binding protein Z than do those bound to the highest affinity binding sites (Goresky et al., 1978). Thus, a higher serum FFA/albumin molar ratio results in more rapid exchange of fatty acid than a lower one (Spector et al., 1965). During pneumococcal sepsis in rats, serum FFA and albumin concentrations are both significantly reduced, but the FFA/albumin molar ratio is similar to that observed in the fasted control rat (Wannemacher et al., 1979c). Thus, even though circulating FFA concentration is reduced, rates of hepatic uptake of this metabolite may be unaltered. These studies emphasize that serum FFA concentrations do not appear to correlate with the rates of release or utilization of FFA and that the FFA/albumin molar ratio may be a better indicator of this process.

B. *Triglycerides*

In general, serum triglycerides tend to be elevated in gram-negative infections and endotoxemia in man and experimental animals (Gallin et al., 1969; Fiser et al., 1972a, 1974; Kaufmann et al., 1976a). In sequential studies during sandfly fever in human volunteers, Lees et al. (1972) found that serum triglycerides were decreased during the illness and elevated during the recovery phase of this infection. Increases in serum triglycerides have also been observed in viral hepatitis and in dogs infected with distemper virus (Beisel and Fiser, 1970). Elevated serum triglycerides could be related to increased synthesis and release of lipid from liver and/or decreased removal of lipids from the circulation.

During various infectious diseases, intracellular fat has been often found to increase in liver and other tissues, with the resulting fatty metamorphosis of these cells (Beisel and Fiser, 1970). Perfused livers from infected rats incorporated more radioactivity from labeled long- or medium-chain fatty acids into intracellular fat than did those from fasted controls (Wannemacher et al., 1979c). In addition, serum VLDL (transport lipoprotein for triglycerides which are formed predominantly in liver) was observed to increase during the convalescent phase of viral infection in humans (Lees et al., 1972), viral hepatitis, gram-negative bacterial infection in patients (Gallin et al., 1969) and during gram-negative sepsis in the rhesus monkey (Kaufmann et al., 1976a). All these observations suggest an increased hepatic synthesis of lipoproteins during various bacterial and viral infections, which could be correlated with elevated serum triglyceride concentrations.

Kaufmann et al. (1976a) have observed a decreased clearance of an oral or

intravenous lipid load in monkeys infected with either *Salmonella typhimurium* or *S. pneumoniae*. This effect was much more marked during gram-negative sepsis and could also be observed when monkeys were injected with *S. typhimurium* endotoxin (Kaufmann et al., 1976b). These observations suggest that lipid disposal mechanisms were impaired particularly during gram-negative sepsis and may thus significantly contribute to the observed elevations in serum triglyceride concentrations. These decreases in lipid disposal were correlated with a reduction in the plasma postheparin lipolytic activity (PHLA) in the infected monkeys (Kaufmann et al., 1976a). Similar decreases in plasma PHLA have been observed during viral hepatitis (Treffot et al., 1978) and in patients with predominantly inflammatory diseases (Gäng et al., 1977). Thus, the reduction of plasma PHLA appears to be a generalized response to infectious disease which could influence serum triglyceride concentration. Therefore, elevated serum triglycerides in various infections appear to be the result of a combination of increased hepatic synthesis and reduced lipid disposal.

C. *Cholesterol*

Changes in serum cholesterol do not have a characteristic pattern for all infections, but tend to reflect the etiology of infectious organisms as well as the stage and severity of infectious illness (Beisel and Fiser, 1970). During sequential studies in the monkey, serum cholesterol was decreased during pneumococcal sepsis and in the early stages of *S. typhimurium* infection, but tended to be elevated during the latter recovery stages of the gram-negative infection (Fiser et al., 1972a). In human volunteers, a mild viral infection resulted in significant decreases in serum cholesterol during the illness and recovery stages of illness (Lees et al., 1972). During viral hepatitis B, serum cholesterol concentrations progressively declined after hepatic inflammation developed; but with the onset of jaundice, serum cholesterol rose abruptly and fecal bile secretion decreased markedly (Saudek, 1977). During a serial study of a group of 10 patients, similar decreases in serum cholesterol were observed at the onset of acute viral hepatitis (Pedroni et al., 1978). The decrease in serum cholesterol prior to development of icterus is presumably related to decreased hepatic synthesis of cholesterol, while the later increase at the onset of jaundice presumably reflects the biliary obstructive stage of viral hepatitis (Saudek, 1977). The latter conclusion is supported by decreased secretion of fecal bile acids and neutral steroids as well as the marked increase in nonesterified serum cholesterol. Despite a normal or slightly reduced concentration of serum cholesterol, Fiser et al. (1971) observed an increase of cholesterogenesis and rates of degradation during either *S. pneumoniae* or *S. typhimurium* infection in the rhesus monkey. Also, increased rates of cholesterol synthesis have been observed in isolated hepatocytes from liver of rats infected with *S. pneumoniae* (Canonico et al., 1977). All of these observations support the conclusion that

alterations in plasma cholesterol do not represent a generalized response to infectious illness, but are the algebraic sum of organism-specific effects on target organs and alterations in rates of cholesterol turnover.

D. *Phospholipids and glycolipids*

In most bacterial infections serum phospholipids are either normal or slightly increased (Beisel and Fiser, 1970). In a sequential study with human volunteers, a mild viral infection resulted in a slight but significant decrease in serum phospholipids when compared to preexposure values (Lees et al., 1972). In general, serum lecithin tended to be elevated in most bacterial infections in man and experimental animals (Beisel and Fiser, 1970). Alterations in serum phospholipids and glycolipids in general reflect infection-related changes in rates of synthesis and utilization of these lipid moieties.

E. *Lipoproteins*

Lipoproteins are the major carriers of tissue-synthesized triglyceride, cholesterol and phospholipids in the circulation of mammals. In those infections that result in a significant elevation in serum triglycerides, there is a concurrent rise in VLDL (Fiser and Beisel, 1970; Lees et al., 1972; Fiser et al., 1972a). The major carrier of cholesterol, low-density lipoprotein (LDL) (β-lipoprotein), in general is unchanged or slightly elevated in most infectious diseases (Beisel and Fiser, 1970). However, Lees et al. (1972) observed marked decreases in the cholesterol content of this lipoprotein during mild viral infection in human volunteers. Serum high-density lipoprotein (α-lipoprotein) concentrations were not altered during sandfly fever virus infection in human volunteers (Lees et al., 1972) but its concentration rapidly decreased with the onset of acute viral hepatitis in patients (Pedroni et al., 1978). In addition, lipoproteins with abnormal unesterified cholesterol and phospholipid composition (LPX) have been described in the obstructive jaundice stage of viral hepatitis (Seidel et al., 1969; Seidel, 1972) and are probably related to lipoprotein which caused defective T lymphocyte E rosette function in patients with viral hepatitis A and B (Chisari and Edgington, 1975; Chisari et al., 1977). In acute hepatitis, changes in serum lipoprotein content are probably related to hepatic inflammation and damage produced by this organism. Thus, alterations of the serum concentration of lipoprotein did not appear to be related to a generalized inflammatory response, but were affected mainly by the interaction of the microorganism in the specific tissues of the host.

F. *Ketone bodies*

Ketone bodies (acetoacetate and β-hydroxybutyrate) are synthesized in liver, mainly from fatty acids, and are carried by the bloodstream to extrahepatic

tissues, where they are utilized as energy substrates via oxidation in the tricarboxylic acid cycle. When calories are adequate, serum ketone concentrations are low (less than 0.5 mM). However, during periods of acute or prolonged caloric deprivation, the body markedly increases its serum concentrations of ketones (to 2—3 mM), which are utilized as a source of energy by tissue such as brain (Cahill et al., 1971; Neufeld et al., 1976). This ketonemic adaptation to starvation reduces glucose utilization almost by half, which in turn spares body protein by decreasing the rate of usage of amino acids for gluconeogenesis (Cahill et al., 1971).

In man, monkey, or rodent, there is a general failure of ketonemic adaptation to occur during caloric deprivation associated with severe sepsis (Blackburn et al., 1973; Ryan et al., 1974; Border et al., 1976; Neufeld et al., 1976; Wannemacher et al., 1978). The data in Table 1 illustrate the effect of a 48 h fast on the

TABLE 1

EFFECT OF INFECTIOUS DISEASES, ENDOTOXIN AND STERILE ABSCESS ON SERUM KETONE BODY AND INSULIN CONCENTRATIONS IN RATS

Treatment	Ketone bodies (μmol/ml)	Insulin (μU/ml)
Fed	0.500 ± 0.150*	29 ± 1*
Fasted	2.500 ± 0.500	7 ± 1
Endotoxin	1.000 ± 0.100*	13 ± 1*
Turpentine	0.900 ± 0.125*	22 ± 1*
Venezuelan equine encephalomyelitis	0.400 ± 0.100*	12 ± 2*
Francisella tularensis	0.500 ± 0.200*	16 ± 1*
S. pneumoniae	0.750 ± 0.050*	28 ± 2*

*$P \leq 0.01$ compared to fasted.
Endotoxin, *Escherichia coli*, 1 mg, i.p.; turpentine, 1 ml, s.c.; Venezuelan equine encephalomyelitis, $10^{4.3}$ PFU, s.c.; *F. tularensis*, 10^7 CFU/rat, i.p.; *S. pneumoniae*, 10^4 CFU/rat, s.c.

concentration of serum ketone bodies in control rats and those with various bacterial and viral infections, endotoxemia and sterile turpentine abscess. In all of these infectious or inflammation-related illnesses, serum ketone concentrations were markedly below those observed in fasted controls. During *S. pneumoniae* infection in rat, ketone body concentrations were not only decreased in serum, but also in liver (1.5 to 0.2 μmol/g) and brain (0.065 to 0.04 μmol/g) compared to fasted controls. This inhibition of starvation ketosis appears to be related to the severity and duration of clinical illness rather than etiology of inflammatory disease.

Because of the lack of alternative fuels during severe infectious illness, pro-

teins of skeletal muscle and skin are broken down at an increased rate; the resulting amino acids are utilized as a source of energy and as a substrate for gluconeogenesis, ureagenesis and ammoniagenesis (Wannemacher, 1977). Thus, the inhibition of ketonemic adaptation in the infected host can in part explain the marked protein wasting associated with disease (Blackburn, 1977; Wannemacher, 1977).

III. EFFECT OF INFECTIOUS DISEASE ON LIPID METABOLISM

Liver and adipose tissue are key organs involved in the regulation of lipid metabolism. Thus, infection-related alterations in lipid metabolism of either or both of these tissues could markedly affect the energy economy of the other cells of the body.

A. *Adipocytes*

Adipocytes are the major storage sites for triglycerides in the body. During periods of food deprivation, FFA are mobilized in large amounts from adipose tissue and serve as a major energy source for many of the other tissues of the body. Since infectious disease is usually associated with marked anorexia (Beisel, 1977; Wannemacher and Beisel, 1977), mobilization of stored fatty acids would be required to meet increased caloric requirements of the infected host. However, Ryan et al. (1974) noted that during experimentally induced peritonitis in rats, depletion of the epididymal adipose tissue was relatively less than that observed in fasted controls. This observation coupled with decreased circulating FFA concentration led them to conclude that fat mobilization was reduced during peritonitis in the rat. Based on reduced serum FFA concentrations, O'Donnell et al. (1976) also concluded that mobilization of fat storage was reduced in surgical patients with sepsis. These observations led to the postulate that the reduced availability of fatty acids and depletion of the glycogen stores would result in increased utilization of amino acids as a source of energy which could contribute to the excessive nitrogen loss associated with serious infections (Ryan et al., 1974; O'Donnell et al., 1976; Blackburn, 1977).

More recently, Wannemacher et al. (1979c) found similar rates of depletion of epididymal adipose tissue in rats following inoculation of gram-positive *S. pneumoniae* organisms when compared to fasted controls. Both glycerol and FFA production were increased during in vitro incubation of fat pads from fasted rats. However, no significant effects of *S. pneumoniae* infection were observed in these studies compared to fasted controls. Also, the calculated rate of fatty acid esterification was similar in the fat pads from both the control and infected rats. While the anticipated increase in adipose tissue lipolysis and the decrease in percentage of FFA esterified to triglycerides (Vaughan, 1962) were observed in this in vitro study, the lack of infection-related effects on these pro-

cesses could have been masked by the absence of circulating regulatory factors, such as hormones and inflammatory products (Wannemacher and Beisel, 1977). Therefore, total body fat was prelabeled with ^{14}C and rates of labeled CO_2 production were measured during fasting alone or with a superimposed *S. pneumoniae* infection. While fasting increased the rate of $^{14}CO_2$ production and presumably lipolysis, infection plus fasting did not significantly alter this response. Thus, from both in vivo and in vitro studies, it may be concluded that rates of lipolysis of stored body fat were not significantly altered during pneumococcal sepsis in the rat.

In another study, Carpentier et al. (1979) measured glycerol turnover to assess the rate of lipolysis in injured and infected patients. While plasma FFA concentrations were markedly depressed, glycerol turnover rates were elevated 2—3-times normal values in the septic patients. These studies are suggestive of increased rates of lipolysis of body fat in septic patients, but it is also possible that the increased glycerol turnover rate could represent an increase in the futile cycle of glucose-glycerol.

At the present time it is not possible to ascertain clearly the effects of infection on rates of lipolysis of body fat but, in general, it appears that it is either unaltered or slightly elevated in the septic host. Further, the effects appear to be influenced by the severity and duration of infectious illness. The decrease in serum FFA during sepsis in man and experimental animals is apparently the result of the reduction of the concentration of FFA-transport protein (albumin) rather than a depression in the rate of release of fatty acids from adipose tissue. This conclusion would be supported by the depletion of body fat in chronic wasting infections such as tuberculosis (Beisel and Fiser, 1970; Beisel, 1977). The effects of infection on lipid metabolism in adipose tissue are further complicated by observations that certain specialized forms of body fat, brown fat, may be specifically affected during certain infectious diseases (Beisel and Fiser, 1970).

B. *Liver*

The pathways of fatty acid activation, esterification and oxidation in the hepatocyte are shown in Fig. 1. The metabolism of long-chain fatty acids differs from that of medium and short-chain fatty acids in that the latter two traverse the mitochondrial membrane directly, while long-chain fatty acids must be activated to their CoA ester and transesterified to carnitine for transport across the semipermeable inner mitochondrial membrane. The fatty acylcarnitine is then reesterified to CoA on the inner surface of the membrane (Fritz and Yue 1963; Brosnan et al., 1973). The enzymes involved in the activation and transport of long-chain fatty acids into mitochondria are fatty acid-CoA ligase (EC 6.2.1.3) and carnitine acyltransferase I and II (EC 2.3.1.-). Activation of long-chain fatty acid takes place in the cytoplasm. The resulting fatty acyl-CoA is strategically located at the branch-point between fatty acid esterification to trigly-

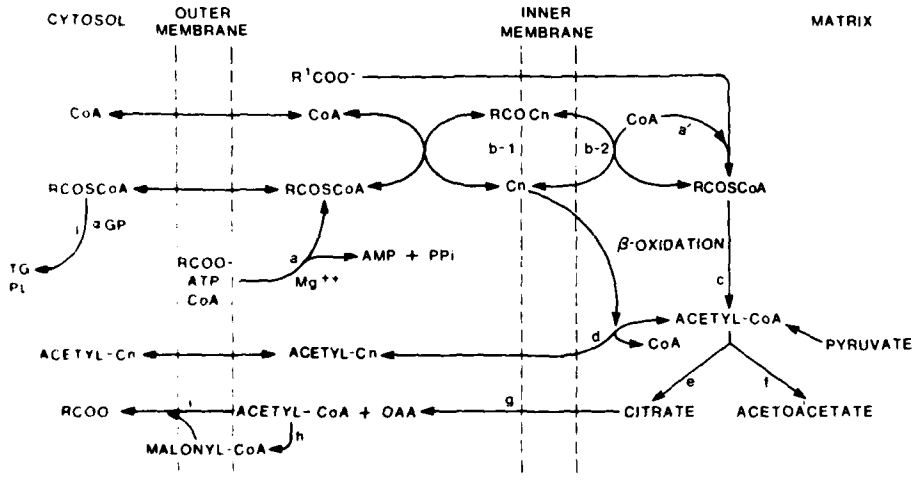

Fig. 1. Pathways of fatty acid activation, oxidation and esterification in hepatocyte. (a) Fatty acid-CoA ligase; (b) carnitine palmitoyltransferase I and II; (c) acyl-CoA dehydrogenase, enoylhydratase, L-β-hydroxyacyl dehydrogenase, thiolase; (d) carnitine acetyltransferase; (e) citrate condensing enzyme; (f) ketone body synthesis; (g) citrate cleavage enzyme; (h) acetyl-CoA carboxylase; (i) fatty acid synthetase; (j) α-glycerophosphate acyltransferase; TG, triglyceride; PL, phospholipid; R, long-chain, ≥ 12 C atoms; R¹, short- and medium-chain, < 12 C atoms; Cn, carnitine; αGP, α-glycerophosphate; OAA, oxaloacetate.

cerides and transport into mitochondria to oxidative pathways. The shuttling of fatty acyl-CoA into the synthesis of triglyceride and the acylation of carnitine is considered one of the major regulatory branch-points of fatty acid metabolism in the hepatocyte.

Once fatty acids enter the mitochondria via the carnitine acyltransferase enzyme system, they are reesterified to the CoA ester which may then undergo β-oxidation. β-oxidation involves the successive removal of acetyl-CoA units from fatty acyl-CoA. Acetyl-CoA formed during this oxidation is subsequently available to enter the tricarboxylic acid cycle for complete oxidation to CO_2 and H_2O or to proceed through hydroxymethylglutaryl-CoA to form acetoacetate. Acetyl-CoA may also leave the mitochondria via citrate or as acetylcarnitine. Citrate is cleaved in the cytosol, reforming acetyl-CoA which can then be utilized for the production of new fatty acid and/or cholesterol. Peroxisomes can also oxidize fatty acids via β-oxidation to form acetyl-CoA, which leaves the peroxisomes as acetylcarnitine. But unlike mitochondrial oxidation, peroxisomal oxidation is not stoichiometric and appears to be specific for long-chain fatty acids (Lazarow and De Duve, 1976). Cytoplasmic acetylcarnitine as such cannot enter other metabolic pathways but must be reesterified to acetyl-CoA.

During most infections studied to date there has been a marked decrease in serum and hepatic ketone body concentrations relative to fasted controls (Blackburn et al. 1973; Neufeld et al., 1976; Blackburn, 1977). Ketone bodies

are produced by the liver when excessive fat is available for β-oxidation and when glucose availability is limited (Cahill et al., 1971). In turn, the amount of ketone bodies in the bloodstream is dependent on the balance between their rate of synthesis by the liver and their rate of utilization by tissues such as muscle, brain and kidney (Owen et al., 1969). The observation that infection or inflammation coupled to starvation caused diminished starvation-induced ketosis (Neufeld et al., 1976; Blackburn, 1977) was investigated further in rats infected with *S. pneumoniae* or *Francisella tularensis*. Wannemacher et al. (1979c) determined that the rate of CO_2 production from labeled ketone bodies was either unaffected or reduced during sepsis. Thus, the diminished ketone body concentration observed during infection was the result of decreased production rather than increased utilization of ketone bodies.

The major substrates for hepatic ketogenesis are long-chain fatty acids. The term 'ketogenic capacity' refers to the ability of the liver to produce ketone bodies when provided with a given concentration of long-chain fatty acid. Studies by Wannemacher et al. (1979c) have shown that livers from fasted-infected rats oxidize less oleic acid to ketone bodies and produce more triglyceride from oleic acid compared to fasted controls. Both fasted and fasted-infected rat livers were equally capable of converting medium-chain fatty acids to ketone bodies. There was no difference in the amount of fatty acid taken up by the livers from infected or fasted control rats (Pace et al., 1978). Therefore, despite an adequate exogenous supply of fatty acid, ketogenesis can be regulated by hepatic metabolism of fatty acids.

The net rate of fatty acid oxidation to ketone bodies is influenced not only by substrate availability and enzyme activities, but also more directly by the disposal of acetyl-CoA through ketogenic and nonketogenic pathways. A recent (McGarry, 1979) regulatory model for ketogenesis suggests that factors such as a decreased insulin/glucagon ratio, reduced liver glycogen content, an increased hepatic carnitine content and a decreased malonyl-CoA concentration are prerequisites for the ketotic state.

Cofactors and substrates such as carnitine, CoA and malonyl-CoA have been reported to be regulatory factors for ketogenesis during starvation (Fritz and Yue, 1963; McGarry et al., 1975a, 1977). Bressler and Wittels (1965) reported a possible lack of muscle carnitine involvement in the metabolic response of the guinea-pig to diphtheria toxin; Border et al. (1970) reported that sepsis without starvation caused a decrease in skeletal muscle carnitine. However, a combination of sepsis and starvation is associated with essentially unchanged skeletal muscle carnitine values (Border et al., 1970; Pace et al., 1977). Both in vivo (Pace et al., 1977; Wannemacher et al., 1979c) and in vitro (Pace et al., 1978) studies showed increased hepatic carnitine concentrations during infection despite a reduced rate of ketogenesis, while CoA decreased in livers from these rats (Pace et al., 1978). Hepatic malonyl-CoA decreased in the fasted-infected rat as it did in the fasted rat (Wannemacher et al., 1979c). Therefore, neither reduced carnitine nor elevated malonyl-CoA concentrations could account for

the reduced rate of ketone production during infection. Recent data (Pace et al., 1980; Pace and Wannemacher, 1980) suggest that certain alterations in the subcellular distribution of carnitine and CoA as well as changes in the activities of enzymes involved in fatty acid transport, esterification and oxidation could explain the reduced ketogenesis associated with pneumococcal sepsis.

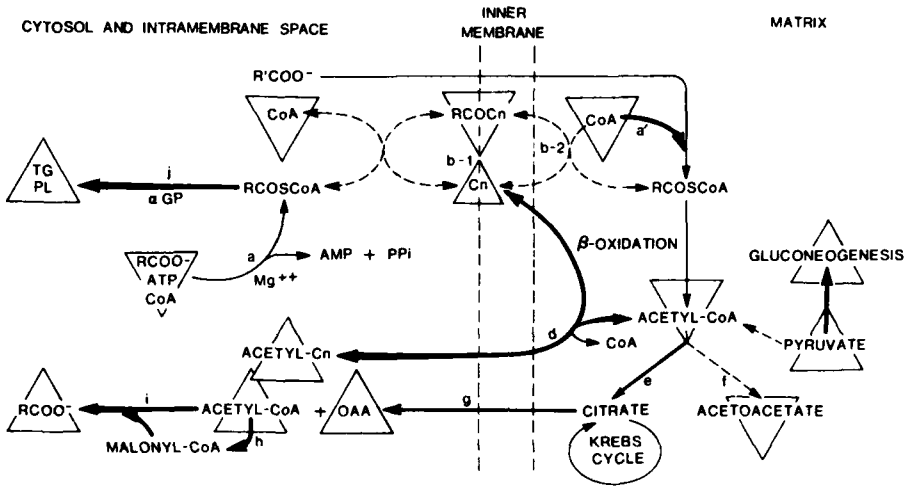

Fig. 2. Alterations of fatty acid metabolism in liver of fasted-infected rats compared to fasted-control rats. Abbreviations are defined in Fig. 1. Increases in concentration of a metabolite denoted by △ and decreases by ▽; elevation in enzyme activity by ⟶ and depressions by- - -→.

These controlling pathways in the fasted-infected rat model are shown in Fig. 2. The fasted-infected rat resembles the fed rat in that long-chain acyl-CoA appears to be directed toward triglyceride synthesis (Pace and Wannemacher, 1980) rather than oxidation. The distribution of acyl groups between the pathways of esterification and oxidation is catalyzed by α-glycerophosphate acyltransferase (EC 2.3.1.15) and carnitine acyltransferase, respectively. Recent data (Pace and Wannemacher, 1980) show that carnitine acyltransferase activity decreases during infections, while the total acylation of glycerophosphate increases compared to fasted control values. These observations suggest that the rate of shuttling of long-chain acyl-CoA into triglyceride synthesis is one of the major regulators of ketogenic capacity of liver.

Within the mitochondria, the enzymes of β-oxidation, the Krebs cycle and acetoacetate synthesis are unaffected by the infectious process (Pace et al., 1977). However, during sepsis, both cytosolic acetyl-CoA and acetylcarnitine increase, while mitochondrial acetyl-CoA decreases (Pace et al., 1980). This information coupled with the changes in enzymic activities observed during the infectious state suggests a shuttling of acetyl-CoA into the cytosol, where carnitine appears to be buffering the active acetyl pool. The net result is a decreased availability of acetyl units for ketone body synthesis within the matrix of the

mitochondria.

Fatty acid (Wannemacher et al., 1979c) and cholesterol (Canonico et al., 1977) syntheses are increased in liver of infected rats. While enzymes such as citrate cleavage enzyme (EC 4.1.3.8) and citrate condensing enzyme (EC 4.1.3.7) have not been determined in the fasted-infected rat, Tubbs and Garland (1964) have reported the effect of starvation alone on these enzymes. The products of the citrate cleavage enzyme, however, have been determined to increase in the fasted-infected rat (Pace et al., 1980). Preliminary studies (Wannemacher et al., 1979c; Pace and Wannemacher, 1980) show that the kinetic rates of acetyl-CoA carboxylase (EC 6.4.1.2) and fatty acid synthetase complex are increased during infectious disease. These enzyme changes are consistent with increased rates of synthesis of fatty acids and cholesterol.

Thus, the combined shuttling of acyl-CoA into triglyceride synthesis and movement of acetyl-CoA out of mitochondria into fatty acid and cholesterol synthesis appear to be responsible for the reduced ketogenic capacity of the liver from infected rats. This, in turn, probably accounts for the reduced ability of an infected patient or experimental animal to develop starvation ketonemia. While the regulator of hepatic ketogenesis has not been completely elucidated, McGarry et al. (1975b) have suggested a bihormonal control by glucagon and insulin. While glucagon has been shown to influence the ketogenic capacity of the perfused liver from fed rats (McGarry et al., 1975b), the antiketogenic effect of insulin on fasted liver has not been demonstrated (Beall and Pace, 1980). However, the elevated serum insulin concentration may play some indirect role in the regulation of ketone production in the infected host (Pace et al., 1978; Neufeld et al., 1980).

IV. EFFECT OF INFECTION-RELATED ALTERATIONS IN HORMONAL BALANCE ON LIPID METABOLISM

The infectious process causes marked alterations in hormonal metabolism and distribution (Chapter 7). The secretion of both so-called 'catabolic' hormones (catecholamines, glucagon and cortisol) and 'prime anabolic' hormone (insulin) is increased during infectious disease (Beisel, 1977). Catabolic hormones, especially catecholamine, have stimulatory effects on lipolysis of adipose tissue, while the anabolic actions of insulin in this tissue favor esterification of fatty acids to triglycerides. Thus, a delicate balance between concentration of the catabolic hormone and insulin can regulate the rate of lipolysis of adipose tissue. In infections, especially those associated with injury, the elevated secretions of catecholamines would be associated with lipolysis of body fat. Indeed, Carpentier et al. (1979) did find high urinary catecholamine output in surgical patients with sepsis. Further, when serum insulin was elevated following glucose infusions, it did not inhibit the catecholamine stimulation of triglyceride breakdown. In contrast, during a milder pneumococcal sepsis in the

monkey, infusion with 25% dextrose solution reduced the FFA/albumin ratio from 1.68 to 0.65 (Wannemacher et al., 1978). This dextrose infusion increased plasma insulin concentrations almost 10-fold, which apparently resulted in inhibition of lipolysis of the adipose tissue. These observations emphasize the important role that the balance between the catabolic hormones and insulin plays in regulating lipid metabolism during infectious disease.

Increased serum insulin and glucagon concentrations during infectious disease have been noted in man and experimental animals by a number of investigators (Shambaugh and Beisel, 1967; Rocha et al., 1973; George et al., 1974, 1977; Ryan et al., 1974; Blackard et al., 1976; Curnow et al., 1976; Neufeld et al., 1976; Rayfield et al., 1977; Kaminski et al., 1979). The data in Table 1 demonstrate the effects that various bacterial and viral infections, endotoxin and turpentine-induced sterile abscess have on peripheral serum insulin content of the rat. In all the experimentally induced infections in rats, maximum elevations of serum insulin are observed before the depression in serum ketone bodies (Neufeld et al., 1980) which could be suggestive of a causal relationship between serum insulin concentration and rate of ketosis. However, during these various infections, the rise of serum glucagon concentration exceeds the elevation in insulin, resulting in a decrease in the insulin/glucagon molar ratio. McGarry et al. (1975b) have suggested a bihormonal regulation of hepatic ketogenesis in which glucagon is stimulatory and insulin inhibitory. Thus, the reduced insulin/glucagon molar ratio in serum of infected rat should have been associated with an elevated rate of hepatic ketogenesis rather than the observed decrease (Wannemacher et al., 1979c). These paradoxical observations have led to suggestions that the inhibitory effect of insulin on hepatic ketogenesis is, in part, independent of serum glucagon concentrations (Neufeld et al., 1980).

Variation in serum concentration of hormones secreted by the thyroid, parathyroid, adrenal cortex, adrenal medulla, or gonads did not appear to alter the infection-induced inhibition of fasting ketosis (Neufeld et al., 1980). An infection induced in diabetic rats did not inhibit the development of fasting ketosis (Neufeld et al., 1980). Further, if insulin was administered to either infected or noninfected diabetic rats, the decrease in the concentration of serum ketone bodies was the same in both groups of rats. In hypophysectomized rats, serum insulin concentrations are below the limits of detection by radioimmunoassay. When an infection was imposed on hypophysectomized rats, there was no inhibition of fasting ketosis (Neufeld et al., 1980). Data such as these suggest a relationship between the rate of insulin secretion and infection-induced depression of serum ketone bodies. However, it has not as yet been possible to demonstrate a direct antiketogenic effect of insulin in the perfused liver from fasted rats (McGarry et al., 1975b; Beall and Pace, 1980). Thus, increased serum insulin could have some indirect role in regulation of rates of hepatic ketogenesis in the infected host (Pace et al., 1978; Neufeld et al., 1980).

V. USE OF LIPID INFUSION DURING INFECTIOUS DISEASE

A. *Protein sparing*

It has been well documented that severe sepsis in man or experimental animals results in marked wasting of body protein, which can lead to the rapid development of the protein-calorie malnutrition syndrome (Beisel, 1977; Wannemacher and Beisel, 1977). The wasting of body protein is associated with the flux of amino acids from tissues such as skeletal muscle and skin to viscera, where they are utilized for gluconeogenesis; synthesis of a large variety of proteins, including those involved in specific and nonspecific host defense mechanisms against infectious disease, acute-phase proteins, production of new white cells, and obligatory protein necessary to maintain homeostasis of the host; and as a direct source of energy (Wannemacher, 1977). Intravenous infusion of amino acids has been shown to spare body protein in patients and experimental animals who became 'keto-adapted' (Blackburn et al., 1973; Miller et al., 1977a; Kaminski et al., 1977; Wannemacher et al., 1978). In contrast, in patients with deep surgical sepsis and in monkeys with severe sepsis, who did not develop starvation ketonemia, intravenous amino acid infusion did not prevent wasting of body protein (Miller et al., 1977b; Wannemacher et al., 1978). During pneumococcal infection, the monkeys that were infused with amino acids alone lost approximately 11% of their body protein over the 6-day study. The addition of 85 cal/kg per day of either dextrose or lipid essentially prevented the infection-stimulated wasting of body protein (Table 2). These observa-

TABLE 2

PERCENT CHANGE IN BODY PROTEIN DURING 6-DAY *S. PNEUMONIAE* INFECTION IN RHESUS MONKEY

Group	Nutrient support	%
1	Amino acids (0.55 g/kg per day)	$-11.01 \pm 2.22^{b,c,d,e,f}$
2	Amino acids + dextrose (85 cal/kg per day)	$0.92 \pm 0.57^{a,c,f}$
3	Amino acids + dextrose (32 cal/kg per day)	$-5.94 \pm 0.81^{a,b,e}$
4	Amino acids + lipid (85 cal/kg per day)	$-1.41 \pm 0.61^{a,f}$
5	Amino acids + dextrose (32 cal/kg per day) + lipid (50 cal/kg per day)	$1.00 \pm 0.64^{a,c,f}$
6	Amino acids + dextrose (32 cal/kg per day) + glycerol (7.2 cal/kg per day)	$-5.68 \pm 0.40^{a,b,d,e}$

[a] $P < 0.05$ compared to group 1.
[b] $P < 0.05$ compared to group 2.
[c] $P < 0.05$ compared to group 3.
[d] $P < 0.05$ compared to group 4.
[e] $P < 0.05$ compared to group 5.
[f] $P < 0.05$ compared to group 6.

tions on the ability of the septic host to utilize lipids as a calorie source are in agreement with those of a number of investigators (Yeo et al., 1973; Zohrab et al., 1973; Deitel and Kaminsky, 1974; Hansen et al., 1976; Jeejeebhoy et al., 1976; Silberman et al., 1977). In contrast, Long et al (1975) found a greater protein-sparing effect of glucose as compared to fat in burn patients and related this to insulin response elicited by glucose. In other studies (Woolfson et al., 1979; Allison, 1980), this intravenous infusion of a solution, in which 42% of the nonprotein calories were supplied by fat emulsion and the remainder by sorbitol and glucose, resulted in slightly less protein sparing in patients with surgical trauma or burns than when all the nonprotein calories were supplied by glucose. When insulin was added to the glucose infusion, serum insulin values were between 100 and 300 μU/ml and there was a significant improvement in protein sparing compared to glucose infusion without added insulin. Thus, it was concluded that a circulating concentration of 200—300 μU/ml of insulin is required to reduce protein wasting in a highly catabolic patient. In contrast, lipid infusion results in low serum insulin concentrations, which could (Woolfson et al., 1979; Allison, 1980) explain its reduced protein-sparing effects in these patients. To test this hypothesis, monkeys were infused with a suboptimal caloric intake of dextrose (32 cal/kg per day) plus amino acids during pneumococcal sepsis (Wannemacher et al., 1979b). Intravenous infusion of this solution resulted in plasma insulin concentrations of 100—300 μU/ml, but the monkeys still lost approximately 6% of their body protein during the 6-day course of pneumococcal infection (Table 2). Intravenous infusion of 55 cal/kg per day from Intralipid along with this dextrose/amino acid solution essentially prevented protein wasting during pneumococcal sepsis in the monkey (Table 2). Thus, even in the presence of markedly elevated circulating insulin concentrations, the septic monkey was able to utilize infused lipids as a source of calories. Similar protein-sparing effects of lipids have been observed by Vinnars et al. (1979), when severely traumatized or burned patients were infused intravenously with a solution in which 50% of the nonprotein calories were supplied by fat emulsion with the remainder coming from dextrose.

In the fat emulsion approximately 13% of the caloric content comes from glycerol, which is both free in solution and part of the triglycerides. Brennan and co-workers (1975) concluded that the nitrogen sparing associated with the infusion of fat emulsion in fasting man was associated with the glycerol content of this solution. Similarly, McDougal et al. (1977) suggested that the glycerol content of the fat emulsion was the major calorie source utilized by burned patients. However, when monkeys were infused intravenously with a solution in which glycerol supplied 7.2 cal/kg per day (equivalent to that contained in 55 cal/kg per day of lipid emulsion) plus dextrose (32 cal/kg per day) and amino acids, the loss of body proteins during pneumococcal sepsis was not significantly altered compared to monkeys infused with dextrose/amino acid mixture (Table 2). Thus, the protein-sparing effect of infused lipid emulsion does not appear to be related to its glycerol content. All these observations suggest that

the septic patient or monkey is able to utilize intravenously infused lipids to meet its caloric requirements, but the efficiency of utilization may be less than that of an isocaloric infusion of dextrose. This, in part, may be related to the reduced ability of the septic host to convert the infused fatty acids to ketones (Wannemacher et al., 1978).

B. *Lipid clearance*

Since sepsis, especially endotoxemia, affects lipid clearance and plasma heparin lipase activity, it was anticipated that infusion of lipid emulsion could have marked effects on serum lipid concentrations in the infected host. Jeejeebhoy et al. (1976) found that lipid infusion in seriously ill surgical patients caused a slight increase in serum triglycerides and a marked elevation in serum cholesterol. During pneumococcal sepsis in the monkey, infusion of lipid emulsion at 85 cal/kg per day resulted in marked elevations of plasma triglycerides, FFA and cholesterol (Wannemacher et al., 1978). When the infusion of lipid emulsion was reduced to 50 cal/kg per day plus dextrose and amino acids, plasma triglycerides and FFA were not significantly elevated during *S. pneumoniae* (gram-positive) or *S. typhimurium* (gram-negative) infection in the monkey (Fig. 3). In contrast, plasma cholesterol was progressively elevated during both gram-positive and gram-negative sepsis in the monkey. During oral (enteral) nutrient support in the monkey with a solution that supplied approximately 35 cal/kg per day from lipid (Wannemacher and Dinterman, 1979), plasma triglycerides and cholesterol were slightly, but not significantly, elevated during both *S. pneumoniae* and *S. typhimurium* infection (Fig. 4). Plasma FFA were significantly elevated during enteral nutrition in monkeys with an *S. typhimurium* infection (Fig. 4). Thus, both intravenous and oral infusion of lipids do have marked effects on circulating lipid concentrations, with elevations in plasma cholesterol being the most consistent finding. This increase in plasma cholesterol could represent a shuttling of the two carbon fragments from fatty acid oxidation into cholesterol synthesis. The alteration in circulating lipid content appears to be a function of both the rate of lipid infusion and a severity of illness associated with infectious diseases.

C. *Visceral protein synthesis*

Nitrogen balance merely reflects the algebraic sum of rates of protein metabolism in various tissues of the body. Serum albumin concentrations have been utilized as an indicator of protein metabolism in the viscera of the body (Bistrian, 1977). Despite slightly better nitrogen retention during pneumococcal sepsis in monkeys infused with amino acids and dextrose, plasma albumin concentrations declined over the 6-day experimental period. In contrast, during intravenous infusion of amino acids plus lipid, plasma albumin concentrations were not significantly altered in the septic monkey (Wannemacher et al., 1978).

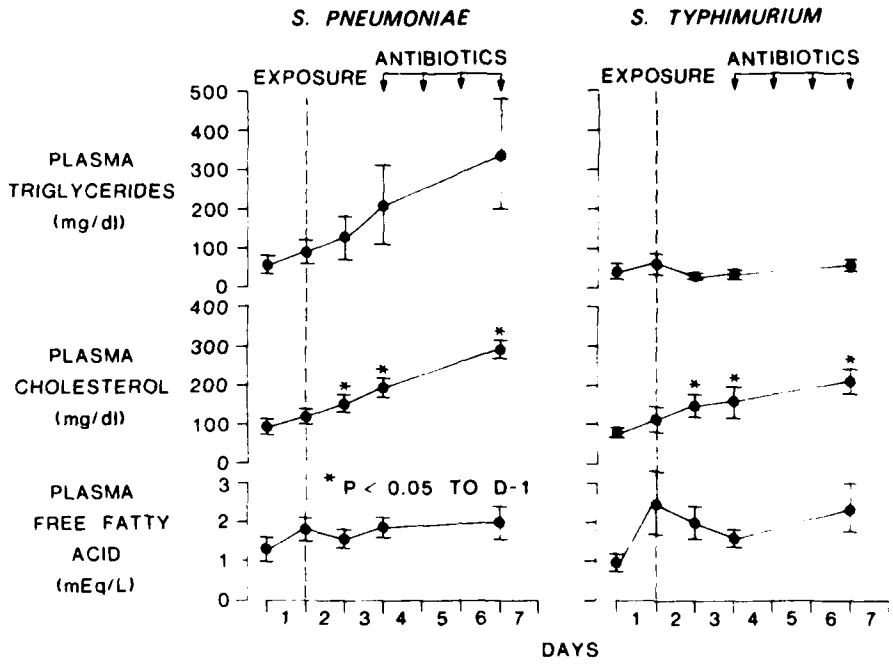

Fig. 3. Sequential changes in plasma lipid concentration in septic monkeys receiving an intravenous infusion of 0.55 g of amino acid nitrogen, 32 cal from dextrose and 50 cal of lipid/kg per day.

Further, plasma haptoglobin, an acute-phase protein (Bostian et al., 1976), increased at a faster rate in septic monkeys infused with amino acids plus lipid compared to those receiving amino acids plus dextrose. It is well established that insulin reduces mobilization of peripheral fat and stimulates sequestering of amino acids in muscle and synthesis of muscle protein (Munro, 1964; Bistrian, 1977). This metabolic response to insulin directs the flow of amino acids and energy substrates away from visceral cells responsible for serum protein synthesis and immune functions Thus, it has been hypothesized that the increased insulin secretion following dextrose infusion is responsible for the rapid fall in serum albumin, reduced rate of albumin synthesis and decreased immune function in patients and experimental animals which are experiencing catabolic stress from surgery, trauma, or infection (Bistrian et al., 1975; Skillman et al., 1976; Bistrian, 1977; Wannemacher et al., 1978). In contrast, intravenous infusion of lipid and amino acids does not stimulate secretion of endogenous insulin (Jeejeebhoy et al., 1976; Wannemacher et al., 1978; Woolfson et al., 1979; Allison, 1980) and therefore allows normal stress-related catabolic response of increased mobilization of peripheral fat and release of amino acids in skeletal muscle. Under these conditions, the visceral cells of the traumatized and/or septic individual could have sufficient amino acids and energy substrates to meet the requirements for synthesis of secretory proteins

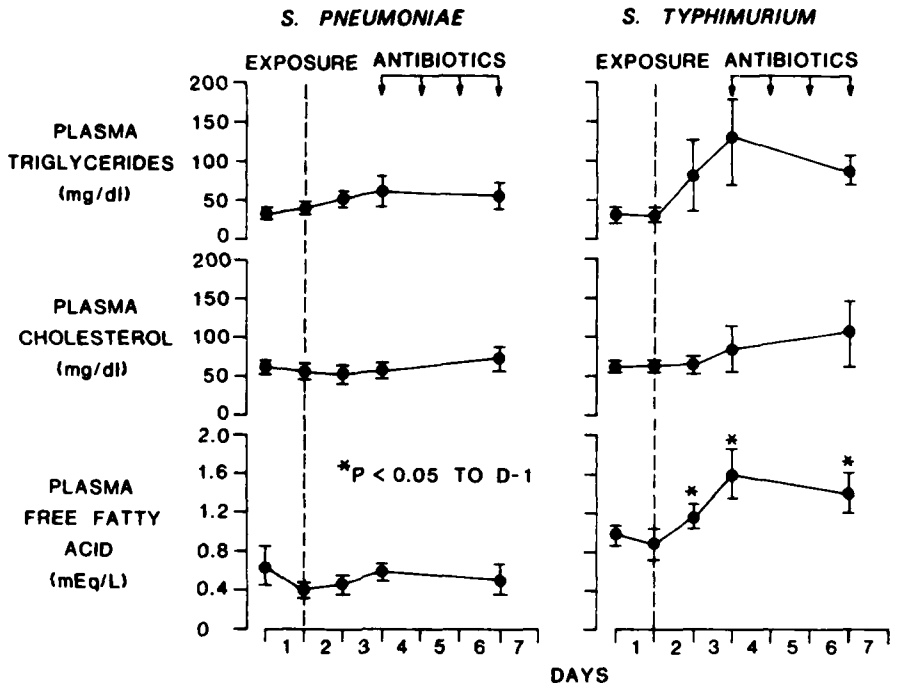

Fig. 4. Sequential changes in plasma lipid concentration in septic monkeys receiving an oral infusion (enteral nutrition) of 0.55 g of protein nitrogen, 55 cal from complex carbohydrates, and 32 cal from fat.

and a normal immune response. These observations suggest that perhaps other criteria besides prevention of wasting of body protein should be considered in determining an optimum nutrient support therapy for maximizing host defense against infectious disease.

D. *Ketosis*

Livers from infected rats have decreased ketogenic capacity compared to fasted controls (Wannemacher et al., 1979c). However, monkeys infused intravenously with lipid plus amino acids were able to maintain starvation ketonemia during pneumococcal sepsis, but urinary excretion of β-hydroxybutyrate was significantly reduced when compared to control monkeys receiving similar intravenous nutrient support (Wannemacher et al., 1978). Thus, the liver of the infected monkey was able to utilize an exogenous supply of fatty acids to synthesize ketone bodies, but at a slightly reduced rate as reflected in the lower concentrations of urinary ketones. This may, in part, explain why lipid was a slightly less efficient calorie substrate than dextrose in isocaloric infusion during pneumococcal sepsis in the monkey (Wannemacher et al., 1978).

E. *Carbohydrate metabolism*

Studies in patients and experimental animals have demonstrated an increase in glucose synthesis, turnover and oxidation rates during injury and sepsis (Long et al., 1971; Wannemacher et al., 1980). This increase in glucose synthesis appears to be correlated with substrate production and release from skeletal muscle, as well as with elevation in the kinetic rate of gluconeogenesis (Wannemacher et al., 1980). Further, in severe sepsis, the gluconeogenic response as measured by conversion of ^{14}C-labeled alanine to glucose cannot be suppressed by intravenous infusion of dextrose solution (Long et al., 1976; Wannemacher et al., 1979a). During the illness phase of pneumococcal sepsis in the monkey, glucose production and utilization were significantly elevated in monkeys infused with lipids plus amino acids, but the magnitude of the response was significantly less than that observed in the monkeys receiving only intravenous amino acids (Wannemacher et al., 1979a) Thus, exogenous lipids from intravenous infusion could be utilized to meet some of the increased energy demands for the septic host, and thus, reduce the need to break down body protein and utilize amino acids as gluconeogenic substrates. While nutrient infusions appear to influence glucose and alanine kinetic rates in both septic and nonseptic monkeys, they did not appear to influence the infection-related elevation in the kinetic rate of gluconeogenesis. This latter response appears to be related to the elevated glucagon concentrations in septic patients and experimental animals (Wannemacher et al., 1979a).

F. *Immune response*

Overnutrition and obesity in the dog, as well as hyperlipidemia in rabbits, result in decreased resistance to various bacterial and viral infections (Newberne, 1966; Newberne et al., 1969; Fiser et al., 1972b; Yadav et al., 1977). Furthermore, genetically obese mice were observed to have impaired cellular immunity (Meade et al., 1978). More recent studies have demonstrated that polyunsaturated fatty acids can regulate lymphocyte reactivity and may depress the immune system (Mertin and Hughes, 1975; McHugh et al., 1978). Since fat emulsions utilized in intravenous alimentation consist of a mixture of neutral triglycerides of predominantly unsaturated fatty acids, it is possible that utilization of this isotonic caloric source could have some immunosuppressive effects on the immune system.

Finally, as opposed to the direct effect of fatty acids on the immune response, hypercholesterolemia and certain serum lipoproteins can influence the immunocompetence of the host and decrease resistance to infection (Chisari and Edgington, 1975; Chisari et al., 1977; Curtiss and Edgington, 1978; Kos et al., 1979). Since intravenous infusion of lipid emulsion in patients and monkeys stimulated a consistent increase in serum cholesterol and perhaps some

changes in lipoprotein composition (Jeejeebhoy et al., 1976; Wannemacher et al., 1978), it could exert some indirect influence on the immunocompetence of the immune response, which perhaps affects resistance to infection. Because of these recently demonstrated immunosuppressive properties of unsaturated fatty acids and serum lipids, several preliminary studies have been conducted on the effects on lipid emulsion on lymphocyte reactivity. Ota et al. (1977) found that during in vitro phytohemagglutinin or varidase stimulation of lymphocyte transformation, the addition of lipid emulsion in physiological or pharmacological concentrations increased slightly the mitogenic and anergic response of human lymphocytes. These authors concluded that intravenous infusion of this lipid emulsion might not depress immunocompetence of the host. Also, Schole et al. (1978) observed increased survival rate and resistance to various parasitic infections in rats and chickens fed a high-fat diet. In addition, high-fat diet appears to increase phagocytic activity and stimulates the immune system. In contrast, Ladisch et al. (1978) observed that the response of human peripheral blood leukocytes to nonspecific mitogens, such as phytohemagglutinin was virtually unaffected by various concentrations of lipid emulsion, but that the response to specific antigens and allogeneic cells was markedly inhibited in a dose-related manner by lipid emulsion. In addition, serum obtained from patients receiving infusions of lipid also caused up to 100% suppression of the response of normal peripheral blood lymphocytes to the specific antigens and allogeneic cells. These authors concluded that there may be a possible adverse effect on immunological function in patients infused with lipid emulsion. From these contradictory studies, it is obvious that at the present time no clear-cut conclusions can be drawn as to the effect of intravenous lipid infusion on the immunocompetence of an infected patient. Before any conclusions can be drawn as to the effect of intravenous and oral infusion of predominantly polyunsaturated fatty acids on the immunocompetence of a patient, additional studies will be required in which carefully developed and standardized methodologies can be used to evaluate the effects of these nutrients.

VI. CONCLUSIONS

Infectious disease affects serum lipids, but the changes are extremely variable and are not a stereotypic response to inflammation. This is in marked contrast to alterations in protein metabolism which are characteristic of most infectious diseases (Beisel, 1977; Wannemacher and Beisel, 1977). In contrast, infection-related changes in serum lipid profiles appear to vary with the stage and severity of illness, causative microorganism, specific cellular-microorganism interactions and the presence or absence of bacterial toxin. While no infection-related stereotypic pattern of response was observed in serum lipids, the inability of the infected host to develop starvation-induced ketonemia has been

observed in bacterial and viral infections, endotoxemia and turpentine-induced inflammation. This suggests that this inhibition of starvation ketonemia is a characteristic response to infectious disease and inflammation.

The decreased ability of the infected host to develop ketonemic adaptation to starvation can in part account for the marked protein wasting associated with this disease. During infectious disease, the liver has reduced ability to utilize long-chain fatty acids for synthesis to ketone bodies compared to fasted controls. This reduced ketogenic capacity of the liver of an infected host appears to be a combined effect of shuttling of long-chain fatty acid-acyl-CoA into triglyceride synthesis and movement of acetyl-CoA out of mitochondria into fatty acid and cholesterol synthesis. This response may in part be related to an infection-induced elevation in serum insulin concentration, which may play some indirect role in the regulation of ketone production.

The septic individual is able to utilize intravenously infused or orally supplied lipid to meet its caloric requirements, but efficiency of utilization may be less when compared to an isocaloric infusion of dextrose. This reduced efficiency may in part be related to decreased ability of the septic host to convert long-chain fatty acids to ketones. When lipid emulsions are infused intravenously in septic patients or monkeys, serum cholesterol and triglycerides are elevated, but the magnitude of the response appears to be related to both the rate of lipid infusion and severity of infectious illness. However, the infected host can utilize infused lipids for ketone synthesis at a reduced rate, and will reduce glucose utilization when supplied with exogenous fats. Further, lipid calories appear to favor synthesis of visceral proteins, while dextrose calories promote synthesis of muscle proteins. Thus, it appears that infused lipid could favor synthesis of immune proteins involved in host defense against infectious disease. On the other hand, contradictory results have been obtained on the immunosuppressive effect of infused lipid emulsion. At the present time, however, it appears that intravenously or orally infused lipid can be utilized to meet some of the caloric requirements of the critically ill patient who is septic.

Note

The views of the authors do not purport to reflect the positions of the Department of the Army or the Department of Defense.

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